Correlation of Genito-Urinary and General Tuberculosis

CARL R. HOWSON, M.D., and ELLIOT A. ROUFF, M.D., *Los Angeles*

SUMMARY

Genito-urinary tuberculosis is considered to be a local manifestation of a generalized tuberculous infection which, for all practical purposes, has gained entrance to the body through the respiratory tract. Even though clinical or roentgenographic evidence of the pulmonary infection is found in only a small percentage of cases, the problem must be attacked as a whole.

Indolent or inactive disease in other parts of the body may become reactivated as the result of surgical intervention or severe complicating infection.

The importance of thorough general antituberculosis treatment in every case cannot be overemphasized.

AS tuberculosis is a generalized infection with focal manifestations most often in the lungs but not infrequently elsewhere in the body, evaluation of the problem of tuberculous lesions in the genito-urinary tract by physicians primarily interested in the medical aspects of pulmonary tuberculosis is quite in order. Directing treatment entirely at lesions at one site while ignoring the possibility of tuberculosis elsewhere may reduce a patient's chance of satisfactory recovery.

The reported incidence (Table 1) of genito-urinary tuberculosis depends upon whether the patients observed had active pulmonary tuberculosis, active extrapulmonary tuberculosis, or inactive or unapparent pulmonary tuberculosis. Statistics vary also according to the nature of the material studied —whether it is clinical or pathological, whether it is from general hospitals or from tuberculosis institutions. Much depends, too, upon how completely interested and efficient are the clinicians in searching for the presence of complications which may be symptomatically of minor significance.

MacLean[8] reported an incidence of 1 to 2 per cent observed in routine autopsies and of 5 per cent in cases in which there was active pulmonary tuberculosis. He cited reports noting up to 70 per cent incidence of genito-urinary lesions in cases in which there was active extrapulmonary tuberculosis. Bell[3] stated that "tuberculosis of the kidneys is one of the common diseases coming to the attention of urologists but is an infrequent cause of death." He noted renal tuberculosis, exclusive of the miliary form, in 0.22 per cent of autopsies; the incidence of all forms of tuberculosis in persons over one year of age in his material was 8.4 per cent. Miliary renal tuberculosis is observed very frequently at autopsy in cases in which death was caused by pulmonary tuberculosis; incidence of from 20 to 45 per cent has been reported by various observers. Ulcerative renal tuberculosis—that for which surgical treatment may be indicated—is a much less frequent complication; it has been observed at autopsy in from 3.5 to 7 per cent of cases in which the subjects died of pulmonary tuberculosis. In a study of the 1,168,000 patients who were discharged from or died at the Los Angeles County General Hospital between 1918 and 1948, Bogen and Butt[4] noted that in 743 cases (0.06 per cent) death was attributed to genito-urinary tuberculosis. Of some 50,000 patients with active pulmonary tuberculosis, 1.9 per cent had renal tuberculosis at the time of discharge from or death in the hospital; renal tuberculosis was the cause of death in 348 cases (0.7 per cent). In 6,000 of the 40,000 autopsies performed in the 30-year period, evidence of pulmonary and/or extrapulmonary tuberculosis was noted, and renal tuberculous lesions were observed macroscopically in 644 subjects—10.6 per cent of those in which tuberculosis was present. Macroscopic tuberculous lesions of the urinary tract were noted in 20 per cent of cases in which death was attributed to pulmonary tuberculosis. Tuberculosis of the urinary tract was observed in only 4.9 per cent of cases in which pulmonary tuberculosis was present but the patient had died of something else. There were only six cases in which tuberculous lesions were observed only in the genito-urinary tract.

Medlar,[10] in an analysis of postmortem examination of 5,424 male subjects over 16 years of age, at Bellevue Hospital from 1935 through 1944, noted that tuberculous lesions in the genito-urinary system were present in 3.1 per cent of the total number, in 4.5 per cent of the cases in which unhealed pulmonary tuberculous lesions were present but death was from other causes, and in 26 per cent of cases in which pulmonary tuberculosis was the cause of death.

Davenport and Greenleaf,[6] reviewing autopsy reports from Fitzsimons General Army Hospital on 500 consecutive cases in which pulmonary tuberculosis was the primary cause of death, noted that there was also renal involvement in 29.2 per cent of the subjects and genital involvement in 15 per cent. As the average age of patients at Fitzsimons is relatively low, the data might be indicative that the incidence of tuberculous infection of the genito-urinary tract in the younger age groups is higher than it is generally believed to be. Bell,[3] reporting on autopsy in

Presented as part of the Symposium on Genito-Urinary Tuberculosis before the Section on Urology at the 80th Annual Session of the California Medical Association, Los Angeles, May 13 to 16, 1951.

TABLE 1.—*Reported Incidence of Genito-Urinary Tuberculosis Observed at Autopsy.*

	Incidence Per Cent Reported by					
	MACLEAN	MCKENNA	DAVENPORT	BOGEN	BELL	MEDLAR
In routine autopsy	2.0	.....	.....	1.6	0.22	3.1
In subjects with active pulmonary tuberculosis at death	5.0	5.0	.....	5.0	3.5	4.5
When death was caused by pulmonary tuberculosis	10.0	.....	44.0	20.0	.....	26.0
In subjects with active extrapulmonary tuberculosis at death	.....	30-70	.....	.....	.....	.....

133 cases of clinical renal tuberculosis, stated that in 21 instances there was no evidence of pulmonary disease, in 38 there were inactive or healed pulmonary lesions, and in 74 (56 per cent) active pulmonary disease was present. Bell also cited a number of reports by other investigators who, at autopsy, had noted active pulmonary tuberculous lesions in from 30 to 35 per cent of subjects with renal tuberculosis.

In the past the incidence of renal tuberculosis in children has been much lower than in adults because they so often have acute miliary infection with a mortality rate of some 80 per cent in the first two years of life. In the past five years, however, since the advent of streptomycin therapy, the mortality rate has been greatly reduced; and it may be that with the higher survival rate will come an increase in incidence of extrapulmonary tuberculosis in children. Pollock[11] noted renal tuberculosis at autopsy in 1.5 per cent of cases of patients who died on the pediatric tuberculosis service at Sea View Hospital, but in only four of 2,500 subjects examined postmortem on the general pediatric service. On the latter service, however, renal tuberculosis of the kind that is amenable to surgical treatment was proved in five of 312 cases in which the patients had chronic pyuria.

Infection with bovine tubercle bacilli, once the commonest infective organism, now rarely occurs in this country. This is attributed directly to the enforced routine tuberculin skin testing of cattle and the destruction of infected animals.

There are two main portals by which tubercle bacilli enter the body—the digestive tract and the respiratory tract. Tubercle bacilli usually focalize in the lungs and in tracheobronchial lymph nodes, regardless of the portal of entry; whether the respiratory or the digestive tract is the more common portal is still debatable. Less commonly, the bacilli enter through the eye, through an abrasion of the skin, or, in females, through the genital tract.

As Auerbach,[1,2] Thomas[13] and others have brought out, the most generally accepted postulation is that infection of the kidney is hematogenous, because multiple bilateral seeding is commonly observed, because healed foci often are present, and because of the initiation of ulcerative renal tuberculosis by focal rupture into a calyx or collecting tubule. These investigators have cited voluminous evidence to refute the possibility or to establish the extreme rarity of renal infection by way of primary infection from the anterior urethra, direct extension from a neighboring tuberculous process, lymphatic extension from a neighboring lymph node, or ascending infection from the genital organs.

Metastatic infection from pulmonary lesions to distant organs occurs after tubercle bacilli enter the blood stream, which may come about either by direct erosion of a tuberculous focus into a blood vessel, or by way of the lymph stream which may carry bacilli by way of the thoracic duct into the subclavian vein. Bacterial emboli may lodge in the smallest blood vessels in various organs and tissues but clinically manifest lesions do not always develop at the site. It is believed that the factors governing the chance of development of an active lesion are the number and the virulence of bacilli present, the site of the implantation, the presence or absence of local injury or other infection, and the individual's general resistance against tuberculosis. Resistance against such an invasion and attempts at healing may be manifest in any organ, but in some portions of the body these factors are less cogent than in others.

PHASES OF TUBERCULOUS MANIFESTATIONS

The various phases of the manifestations of tubercle bacilli in the human body have many times been likened to those of syphilis. The cycle of events may be described under four headings, dating from the time of invasion by the tubercle bacilli to the most advanced lesions of visceral caseocavernous tuberculosis.

1. The period of incubation — a latent period from the time of original implantation of tubercle bacilli to the appearance of a positive reaction to a skin test with tuberculin.

2. The period of invasion—the time in which the organisms reach the lymphoid system. This is generally a silent phase as far as clinical manifestations are concerned.

3. The period of visceral spread — the time in which, lymphoid resistance having been overcome, implantations of tubercle bacilli reach the various organs by way of the blood stream. The nature of the lesions produced in the tissues by tubercle bacilli depends upon the factors previously enumerated (number and virulence of the organisms, local and general tissue resistance, etc.). The lesions may be sparse or miliary, active or relatively quiescent. Should the original infection be massive, the second phase follows a rapid course and the metastatic foci may become fulminant and rapidly fatal. Should the period of invasion be resisted by the lymphoid sys-

tem, leakage of bacilli into the blood stream will be sparse and infrequent and the metastatic foci rare and slow to develop.

4. The period of advanced caseocavernous tuberculosis. This is the stage of active pulmonary tuberculosis (phthisis) characterized by extensive caseous or ulcerative lesions in the lungs.

As to renal tuberculosis, it would appear that the implantations of tubercle bacilli reach the kidney at a stage in the disease long before the fourth period in which there are gross lesions in the lungs. It is probably in the third stage of tuberculosis, the period of general infection when tubercle bacilli are escaping from the lymphatic system to the blood stream, that the earliest minute foci appear in the kidney. It is in this stage, after lymphatic resistance has been overcome and intermittent hematogenous dissemination of tubercle bacilli is taking place, that implantations occur in the renal cortex which give rise to tubercle bacilluria. As a rule, persons in whom this phenomenon occurs have very nearly, but not quite, overcome the tuberculous infection in its second stage of systemic invasion.

Pathologists, spearheaded by the meticulous work of Medlar over the past 30 years, have traced exactly what occurs when the body is invaded by tubercle bacilli. Save for variations caused by differences in histologic and anatomic structure, tuberculous lesions in the kidney do not differ from those in other organs and tissues of the body. As far as can be determined, the cells that participate in the defensive and reparative processes as regards tuberculous lesions are of the same type in all tissues and organs. The end product of the reparative process is a scar with no indication of the causative factor.

It is not uncommon for a great variety of tuberculous lesions to be present in a single kidney. Mononuclear tubercles, tuberculous abscesses, areas of caseation, scarred areas infiltrated with lymphocytes and with one to many giant cells present, and scars devoid of lymphocytic or mononuclear leukocytic infiltration have all been observed in one organ. From this it would appear that the patient had had, at intervals, showers of tubercle bacilli in the blood stream, and that these showers had been followed by the development of tuberculous lesions in the kidney. The pathologic processes observed in such organs represent, then, lesions of different age and severity, and the scars represent the healed stage in an area where the tubercle bacilli have been overcome. In light of these observations plus the fact that tubercle bacilluria is noted in about 10 per cent of the cases reported without clinical manifestations of renal involvement, it must be agreed that renal tuberculosis with bacilluria can exist without causing symptoms. Rosencrantz and Charnock,[12] in an investigation of 200 men with active pulmonary tuberculosis but with no complaints referable to the genito-urinary tract, noted that there were tubercle bacilli in the urine of 7 per cent of the patients, and that 18 per cent had tuberculosis of the genital tract without bacilluria. It is believed that bacilluria does not exist without ulcerative lesions in the kidney. These lesions are often microscopic and are frequently overlooked. On the other hand, it would seem that renal tuberculosis can exist without bacilluria, judging from the absence of inflammatory exudate and bacilli in the lumen of the tubules in many cases.

Medlar's conception of the pathogenesis of genito-urinary tuberculosis may be at variance with some clinical concepts, but his views must be respected inasmuch as they are based on extremely thorough pathological studies in which the existence of tuberculous disease without significant clinical symptoms was observed. It has been noted that microscopic tuberculous lesions can ulcerate into renal tubules, discharge bacilli into the urine, and then heal completely. Medlar expressed the belief that it is possible for the prostate gland to become infected at the time the urine is contaminated, which could account for the finding, at necropsy, of tuberculosis in the prostate gland of subjects with macroscopically normal kidneys. He said that it could not be assumed that renal lesions never had existed even though the only tuberculous lesions observed were in the genital organs. In Medlar's autopsy series, renal lesions were observed in twice as many subjects as were prostate lesions, and in three times as many as were lesions in other genital organs. Of the renal lesions, 64 per cent were miliary; and involvement of the genital organs in association with miliary renal disease was infrequent. Combined renal and genital tuberculosis was five times more common in subjects with necrotic foci than in those with miliary lesions. These observations suggest that in at least a high proportion of cases in which prostatic involvement occurs, it follows the development of renal lesions. The data also indicate that the prostate gland is the most often affected of the organs in the genital system.

INFECTION OF OTHER GENITAL ORGANS

Although there is general agreement that tuberculosis of the kidney is metastatic and blood-borne, there is no such agreement relative to tuberculous infection of the organs of the genital system, and especially with reference to the relationship of infection in one organ to infection of other organs of the system. Barney[7] expressed the belief that infection is blood-borne to the epididymis, and from there spreads by lymphatic channels to the seminal vesicles and the prostate gland. Young[7] took the view that the first focus in the genital system is in a seminal vesicle, whence the disease spreads to the prostate gland, and then, by lymphatic extension, to the epididymis. Borthwick[5] strongly supported Young's theory of central infection and centrifugal spread, although he took the view, as do many other investigators now, that infection is by bacilluria, reaching the prostate primarily, and that downward spread along the vas to the epididymis is via the lumen and not by lymphatic channels. In support of this view, Borthwick noted that in a very high proportion of all cases of tuberculosis of the genital tract tubercle bacilluria was present at some stage. Also he noted

palpable evidence of prostatic or vesicular involvement in 83 per cent of 237 cases of tuberculous epididymitis, an observation that appears to accord with Medlar's[10] report that in subjects in which tuberculous epididymal lesions were of macroscopic proportions, more than one—and frequently all—of the genital organs were tuberculous. A comparison of the incidence of epididymal tuberculosis with that of tuberculosis of the fallopian tube (recalling that the urinary and genital systems of the female are separated completely) suggests strongly that epididymal tuberculosis is related much more closely to the disease in other organs of the genito-urinary system than to a direct implantation from the blood stream: Tuberculosis of the fallopian tube occurs about as frequently in association with miliary as with necrotic renal lesions, whereas the incidence of epididymal tuberculosis is eight times greater in persons with necrotic or excavating renal lesions than it is in persons in whom the renal disease is miliary.

In the management of patients who have genito-urinary tuberculosis, it must be borne in mind that renal tuberculosis must be related to a primary focus of living bacilli elsewhere in the body. The primary lesion may have occurred in childhood or adolescence. As renal tuberculosis is the result of hematogenous dissemination of tubercle bacilli to the viscera, complete and systematic clinical, laboratory and radiological examinations must be carried out. The presence of extra-urogenital foci of tuberculous infection is particularly likely. If such foci are active, surgical intervention may increase the activity. If they are quiescent, they may remain so during surgical intervention or they may become reactivated, depending upon the virulence of the organisms and the powers of resistance of the patient. Surgeons and physicians managing the conservative treatment must cooperate closely, recognizing the importance of dealing with tuberculosis as a generalized infection. As has so often been emphasized, particularly by urologists who have worked closely with tuberculosis sanatoria, since urologic tuberculosis is chronic and slowly progressive, there rarely is need for rushing into a course of treatment before the condition of the entire genito-urinary tract is determined and attempt is made to locate the primary source of the infection.

1930 Wilshire Boulevard.

REFERENCES

1. Auerbach, O.: Pathology of renal tuberculosis, International Clinics, 3:21, 1940.

2. Auerbach, O.: Pathogenesis of renal tuberculosis, Quart. Bull. Sea View Hospital, 7:122, Oct. 1941.

3. Bell, E. T.: Renal Diseases, Lea & Febiger, 1950, sixth edition.

4. Bogen, E., and Butt, E.: Personal communication. To be published Amer. Rev. of Tuberculosis.

5. Borthwick, W. M.: Modern concepts of genital tuberculosis, Edin. Med. Jour., 53:71, 1946.

6. Davenport, M. C., and Greenleaf, H. M.: Study of 500 autopsies in cases of tuberculosis, U. S. Armed Forces Med. Jour., 2:70, Jan. 1951.

7. Lee, R. O.: Modern views on pathogenesis and treatment of tuberculosis in the male genital tract, Med. Press, London, Nov. 1, 1950, 415.

8. MacLean, J. T.: Genito-urinary tuberculosis, Bull. of Vancouver Med. Assoc., 22:70, Nov. 1945.

9. McKenna, C. M.: Clinical tuberculosis, Goldberg, Vol. 2. F. A. Davis Co., Philadelphia, 1945.

10. Medlar, E. M., Spain, D. M., Holliday, R. W.: Postmortem compared with clinical diagnosis of genito-urinary tuberculosis in male adults, Jour. Urology, 61:1078, June 1949.

11. Pollock, R.: Pediatric genito-urinary tuberculosis, Quart. Bull. Sea View Hosp., 7:126, Oct. 1941.

12. Rosencrantz, E.: Frequency of tubercle bacilluria, Jour. Urology, 44:498, Oct. 1940.

13. Thomas, G. J.: Tuberculosis of the Genito-Urinary System, Fundamentals of Pulmonary Tuberculosis, Thomas, 1949, 385.

14. U. S. Public Health Reports, 65:468, April 17, 1950.